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A Physical Layer Based Assessment Using Serum Markers for the Severity of Liver Fibrosis in Chronic Hepatitis B

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Abstract:

Liver fibrosis levels are critical for accurately diagnosing the severity of chronic liver disease (CLD) and determining the best course of therapy. Since liver biopsy is limited in scope, there is an urgent need for noninvasive and accurate diagnostics that accurately measure liver fibrosis. As a noninvasive, useful, and precise way of evaluating the degree of liver fibrosis by assessing hepatic solidity, ultrasound elastography (US) is widely accepted. Transient elastography, acoustic radiation power drive imaging, supersonic shear-wave imaging, and continuous tissue elastography are only a few of the commercial varieties of US elastography now in use. In spite of the fact that US elastography's poor repeatability remains a major limitation, this method may still be used to diagnose fibrosis in patients with CLD, as long as the results are consistent. Another useful monitoring method that clinicians may undertake at the patient's bedside is US elastography, which can aid in the assessment of lethal entanglements associated with CLD without being obtrusive.

Liver cirrhosis; Hypertension, portal; Ultrasonography; Elasticity imaging methods

Introduction

Chronic liver disease (CLD) has various etiologies, with the viral infection of hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus, alcohol consumption, hepatotoxic drug ingestion, non-alcoholic fatty liver, autoimmune diseases, and cryptogenic hepatopathy being commonly encountered in daily practice. Histologically, liver fibrosis develops and gradually progresses as a result of following a wound-healing response in patients with CLD. In particular, activation of cellular elements including myofibroblasts and stellate cells results in collagen deposition and subsequent development of CLD [1,2]. Liver biopsy is known as the gold standard for diagnosing liver fibrosis. However, liver biopsy also has considerable limitations. The very small size of samples obtained through biopsy may not represent a heterogeneous distribution of liver fibrosis due to sampling bias [3]. In addition, theissue of intra- or inter-observer variability among pathologists in evaluating the grade of fibrosis is an additional limitation because the interpretation process is a subjective and semi-quantified method [4]. According to previous research on chronic hepatitis C, agreement among pathologists regarding the fibrosis grade is not excellent (κ, about 0.5) [5].

Although the rate of complications is very low and the risk has declined with the use of ultrasonographic guidance [6], liver biopsy is somewhat invasive and post-biopsy bleeding can be serious. With respect to non-invasive alternatives to liver biopsy, several serological or biochemical methods for the estimation of liver fibrosis have been validated primarily in patients with chronic hepatitis C, but still lack the ability to identify and classify the intermediate stages of fibrosis [7]. Introduced in 1991, elastography is another non-invasive technique for evaluating the elastic properties of soft tissue either quantitatively or qualitatively [8]. The elastography of the liver is theoretically not easy to determine compared with that of superficial organs because the liver is located deep and under the rib cage. Nevertheless, various techniques of ultrasound (US) elastography have been developed for repeatedly measuring hepatic fibrosis. From a technical standpoint, two types of US elastography for the measurement of liver stiffness are under development: shear wave based elastography and real-time tissue elastography (Fig. 1, Table 1). This review addresses the principles and clinical usefulness of US elastography for the diffuse liver disease with an emphasis on shear wave-based elastography.

Basic Principles of Elastography

Elastography is a promising imaging technique because the elastic modulus of tissues measured by this technique provides the most broad-banded properties compared with other quantitative values

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measured by computed tomography (attenuation value), magneticresonance (MR) imaging (T1 relaxation time), and conventional ultrasonography (bulk modulus). The order of magnitude of the elastic modulus is approximately five times larger than that for other imaging modalities [9], meaning that the use of the elastic modulus can maximize the discrimination between different tissues or between normal tissue and lesions. The elastic modulus is defined as the slope of the stress-strain curve during elastic deformation. Therefore, a stiffer object has a higher elastic modulus.

There are various approaches to elastic imaging, all of which consist of three basic steps: excitation (stress) application, tissue response (strain) measurement, and mechanical parameters estimation [9]. Excitation Application In its most basic form, shear wave-based elastography applies a perpendicular stress force on the target organ to induce "shear" on the tissue (Fig. 2). By definition, shear is the change of shape (displacement)-without a change in volume-produced by a pair of forces acting in opposite directions. At this point, transversely propagating waves with a very low velocity develop in the tissue,

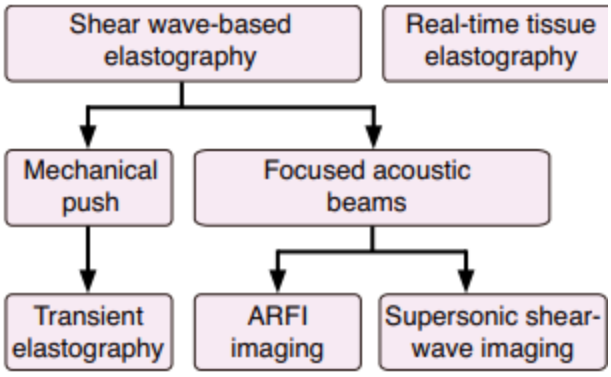

fig. 1. Classification of ultrasound elastography of the liver. ARFI, acoustic radiation force impulse.

Tissue Response Measurement

Measurement of tissue response is the most critical component of elastography. The basic measurement method consists of a comparison of successively obtained images and a reference image (Fig. 2). Through either a mechanical push or acoustic radiation force, the A-axis (direction of force=depth direction) displacement of the target tissue occurs, and the shear waves are generated simultaneously. These are very slow (1-10 m/sec) compared with an US beam and travel perpendicular to the direction of the stress force. To detect a shear wave, two methods using US have been introduced. Transient elastography causes a single transient shear wave to propagate along the A-axis direction by using an M-mode US technique and calculates Young modulus of the tissue by using this information [14]. Another method is the Doppler technique, in which radiofrequency (RF) images including the information of the propagating shear waves are measured using the echo of the transmitted US beams at a very high frame rate, which can be used to generate a tissue displacement map [8,15,16]. Using the tissue displacement maps obtained during the period of shear wave propagation (i.e., less than 14 ms), it is possible to calculate the velocity of a shear wave by analyzing the movement of the peak of the shear wave. In this way, the elastic modulus can be calculated by E=3 ρVs 2 where ρ denotes the density of the tissue and Vs represents the velocity of the shear wave.

Mechanical Parameter Estimation

Both qualitative and quantitative methods are used to perform mechanical parameter estimation (Fig. 2). Liver stiffness is usually

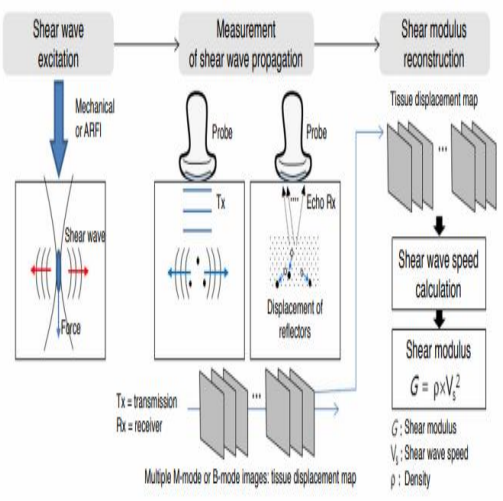

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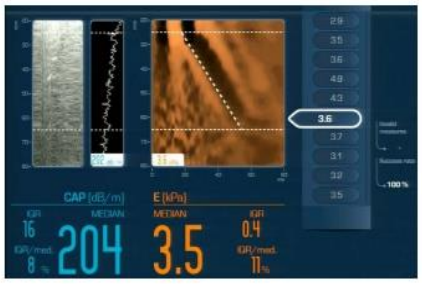
Fig. 2. Diagram depicting the process of shear wave-based ultrasound elastography.

Shear wave-based elastography applies a perpendicular stress force to a target organ in order to induce shear on the tissue. The information on the propagating shear wave including the velocity of the shear wave could be measured by obtaining radiofrequency images with a high frame rate, which can be used to generate a tissue displacement map. Then, the elastic property for quantitative estimation is calculated by the propagating velocity of the shear wave. ARFI, acoustic radiation force impulse.

Methods of Shear Wave-based Elastography

Transient Elastography Transient elastography was the first commercialized elastography method developed to noninvasively assess the stiffness of deep soft tissues such as the liver. Transient elastography consists of two parts: a mechanical vibrator and a single-channel US transducer [14]. The mechanical vibrator generates a low-frequency wave at 50-500 Hz to generate shear stress in the target tissue at a length of 4 cm, and the velocity of the shear wave can then be measured using an US signal (Fig. 3). The most superior advantage of transient elastography is that it has been extensively validated by numerous investigations targeted at patients with CLD, and the results of transient elastography are generally accepted to be well correlated with different stages of liver fibrosis. The validity of liver stiffness measurements are determined by the success rate and the interquartile range divided by the median (IQR/M) in cases with more than 10 valid measurements. Here, the success rate is the ratio of the number of valid measurements to the total number of measurements and should be greater than 60%; IQR/M should be lower than 30% [17]. Despite these advantages, there are several disadvantages of transient elastography. They are as follows: first, transient elastography does not provide a B-mode image, which is essential for accurate targeting. Second, transient elastography is not performed for the patient with ascites. In addition, transient elastography exhibits a relatively high measurement failure rate of 4.5%-6%. Major factors related to this failure rate include a body mass index greater than 28, age over 50 years, non-alcoholic steatohepatitis, diabetes, and a γ-glutamyl-transpeptidase level higher than 57 IU/L [18]. Acoustic Radiation Force Impulse Imaging and Shear Wave Imaging Both ARFI imaging and SSI use focused high-intensity, shortduration acoustic pulses instead of the mechanical vibration of transient elastography in order to produce shear waves in the target tissue [19]. ARFI imaging generates shear waves by a single pushing beam, while shear wave propagation is monitored using conventional pulse-echo US at multiple off-axis lateral locations. By collecting displacement through time information at multiple lateral locations separated by a known distance from the excitation source, the speed of the propagating shear waves can be estimated (Fig. 4). The region of interest (ROI) of ARFI imaging is relatively small (i.e.,



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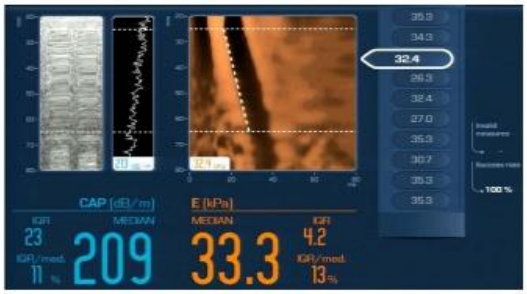

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Fig. 3. Transient elastography of a normal and a cirrhotic patient.

SSI is a new shear wave-based US elastography technique. SSI generates push beams at multiple axial depths to create a nearsupersonic plane wave shear and transmits the unfocused beam (plane wave) to monitor the shear wave propagation throughout the ROI (Fig. 5). The ROI of SSI is fan-shaped and larger than other modalities (up to 50 mm × 50 mm) [20,21]. A remarkable feature of SSI is that it can show viscoelastic properties in all areas in an ROI

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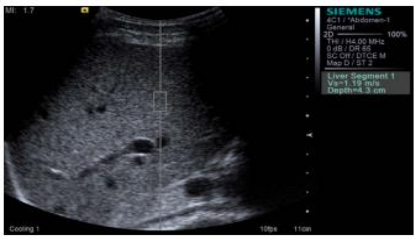
with a color look-up table and thus, is expected to overcome the limitations of transient elastography by which liver stiffness cannot be measured accurately in patients with severe obesity, thick subcutaneous fat, and ascites [22]. Moreover, the same technique



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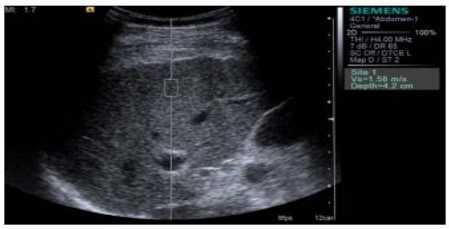

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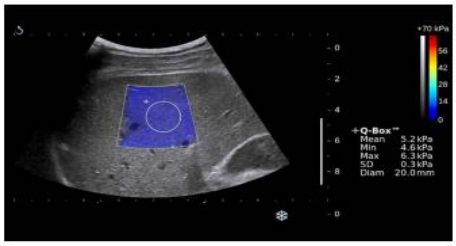
Fig. 4. Acoustic radiation force impulse imaging of a normal and a cirrhotic patient.



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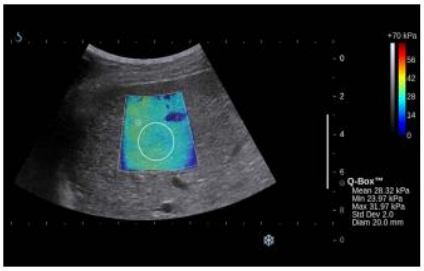

(b)

Fig. 5. Supersonic shear-wave imaging of a normal and a cirrhotic patient

consisting of an excitation application in which the examiner has to compress and relax the body by a transducer or utilize intrinsic stress derived from the heartbeat [12,13]. Simultaneously, echo signals are captured in real time, and the relative stiffness (elastic ratio) of the liver can be calculated along with a real-time color map. Like SSI, real-time tissue elastography can display tissue elasticity images and conventional grayscale US images at the same time but is unable to calculate the elastic modulus (Fig. 6).

Clinical Applications of US Elastography

Hepatic Fibrosis In terms of the diagnostic performance of US elastography for measuring liver stiffness, there have been many clinical studies regarding the diagnosis of hepatic fibrosis using transient elastography [23,24]. According to a recent meta-analysis aimed at chronic hepatitis C patients, the pooled estimate of the cut-off value for significant fibrosis (≥F2 on the METAVIR score system) was 7.71 kPa with a sensitivity of 72% and specificity of 82%. In the case of cirrhosis (F4), the results showed a cut-off of 15.08 kPa with a sensitivity of 84% and specificity of 95%. Another metal analysis of 40 eligible studies showed that the summary sensitivity and specificity were 78% and 80% for significant fibrosis, and 83% and 90% for cirrhosis, respectively (Table 2). In addition, this metaanalysis suggested that transient elastography could be used as a good screening test for cirrhosis, but not for accurately diagnosing fibrotic stages other than cirrhosis because no optimal cut-offs of liver stiffness for individual fibrosis stages have been validated.

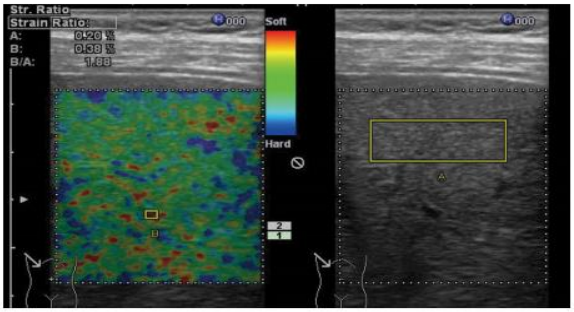

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Fig. 6. Real-time tissue elastography of the liver

Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) actually represents an emerging disease of great clinical interest because of the increasing incidence of metabolic diseases and obesity in recent decades. The disease spectrum of NAFLD is very wide, ranging from simple fatty liver to non-alcoholic steatohepatitis, and liver fibrosis can develop and progress to liver cirrhosis [31]. Although transient elastography is difficult to perform in cases of obesity because subcutaneous fatty tissue attenuates the pushing pulse, its role in causing NAFLD has recently been highlighted owing to the development of a new technique utilizing a vibration-controlled transient elastography device, which allows the calculation of the new controlled attenuation parameter (CAP). CAP is known to be useful for the non-invasive and accurate estimation of liver steatosis [32]. In addition, a new XL probe designed to measure shear waves at deeper positions by using a lower central US frequency (2.5 MHz) can be applied, thereby allowing more reliable results to be obtained compared with conventional M probes.

Follow-up after Liver Transplantation

After liver transplantation, US elastography is also useful to diagnose liver fibrosis caused by relapsed chronic hepatitis and the acute rejection of the liver graft. A systematic review of studies comparing US elastography to liver biopsy for the detection of liver fibrosis by a recurrent HCV infection stated that the diagnostic accuracy for significant fibrosis (F2) using transient elastography was generally good, with a sensitivity and a specificity of 83%. Further, with respect to liver cirrhosis, the sensitivity and specificity were improved to 98% and 84%, respectively [36]. Liver stiffness may also be increased by acute cellular rejection following liver transplantation; however, it is important to keep in mind that liver stiffness can increase in transplanted livers without evidence of rejection since it may undergo ischemic or reperfusion injury within 4 weeks from transplantation, which can in turn result in transient hepatocellular ballooning and hepatocanalicular cholestasis with inflammation that may recover within 2-3 weeks without specific treatment. Therefore, US elastography may be useful to detect rejection at follow-up more than 4 weeks after transplantation [37]. Portal Hypertension Estimation of the severity of portal hypertension in patients with liver cirrhosis is another major use of liver stiffness measurements. Increased portal pressure is the major factor driving the clinical course of cirrhosis. Measurement of the hepatic venous pressure gradient (HVPG) following hepatic venous catheterization was used as a surrogate marker of portal hypertensive stigmata. Recently, there were some investigations concerning the feasibility of the noninvasive measurement of liver stiffness to estimate severe portal hypertension [38,39]. Looking at the results of these studies, we concluded that liver stiffness could be closely correlated with both HVPG and the presence of complications related with portal hypertension (Fig.

8). Roles for Longitudinal Surveillance

To date, the majority of elastography studies have focused on evaluating the cross-sectional performance with respect to the histological fibrosis grade or HVPG. However, an important but undervalued use of elastography is the ability to repeatedly measure liver stiffness. The roles of elastography as longitudinal perspectives with respect to the prediction of the long-term prognosis of the disease and monitoring of clinical courses with or without treatment are well known. In particular, these approaches can be used to non-invasively estimate the prognosis of the patients with fatal complications related to CLD, such as variceal bleeding and decompensation. A longitudinal follow-up of elastography has been proposed as a way to establish the tailored management strategies by providing more detailed prognostic information [40]. For example, the concept of cirrhosis has recently changed from dynamic to bidirectional. In other words, cirrhosis patients may recover if antiviral therapy can be applied properly. At this time, the ideal approach to assess histological outcomes during treatment is serial liver biopsy; however, this is not possible in most cases. Instead, the measurement of liver stiffness by elastography is very useful for

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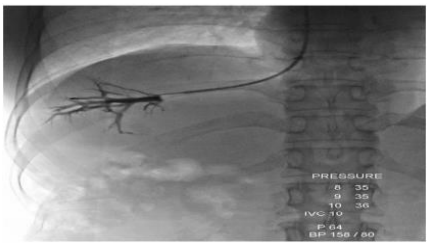
monitoring the changes in liver fibrosis during the antiviral treatment [41,42]. In terms of portal hypertension, elastography may also be used to predict the development of variceal bleeding by using a hybrid parameter, the liver stiffness-spleen diameter to platelet ratio score (LSPS) defined as the product of liver stiffness and the maximum spleen diameter divided by the platelet count [43]. According to risk stratification



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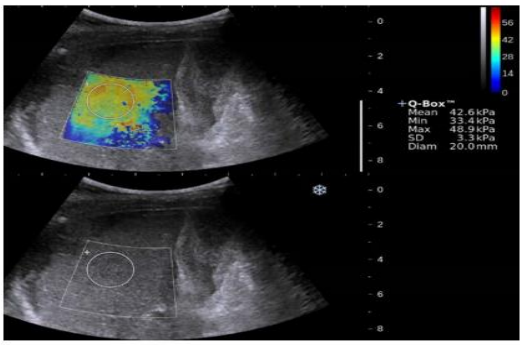

(c)

US Elastography: Weaknesses and Strengths

The most significant challenge facing US elastography is the issue of measurement reproducibility. A number of studies concerning this issue have been published; however, many investigators have brought up questions about this issue due to the inherent limitations of US such as the operator-dependent performance.

Transient elastography is a highly reproducible and user-friendly technique [45], and liver stiffness measurement by transient elastography does not require a learning curve: even a novice can obtain a reliableresult after a single training session [46]. However, because liver stiffness measurements can be influenced significantly by steatosis, obesity, lower degrees of hepatic fibrosis [45], necroinFlammarion of hepatocytes [47], cholestasis [48], elevated central venous pressure [49], and even postprandial conditions [50], it should be carefully applied when used as an alternative measurement of liver stiffness instead of liver biopsy. In the case of ARFI, the overall reproducibility is also not bad, having an intraclass correlation coefficient (ICC) value for the interrater observation of 0.81 and an ICC for the intrarater observation of 0.90. However, gender (women), high body mass index, ascites, and lower degree of liver disease (noncirrhotic patients) are considered factors that impede the reproducibility of ARFI [51]. In the case of SSI, the inter- and intraobserver agreements.

Conclusions

Measurement of liver stiffness is developing to overcome its limits via the use of different technological advancements. Recent publications from the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) have provided a comprehensive guideline for the use of US elastography. Additional information is included in these instructions, such as how to utilise US elastography in practise and how to examine specific body areas. These recommendations state that US elastography may be used to evaluate the degree of liver fibrosis in patients with diffuse liver disease and to discriminate between individuals with nil to moderate fibrosis and those with severe fibrosis, although novel methods must be validated in clinical research. US elastography is currently not suggested for the differentiation of localised hepatic lesions. US elastography may be used to diagnose hepatic fibrosis in patients with CLD, and it can also be used to predict the prognosis of patients with fatal complications associated to CLD. Therefore, an uniform approach for measuring liver stiffness and technical improvements should be a top goal for the clinical use of US elastography in patients. US elastography's clinical utility will be greatly enhanced by these initiatives together.

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